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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/574,386	05/19/2000	Donna G. Albertson	407E-914400US	7843

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EXAMINER	
SPIEGLER, ALEXANDER H	
ART UNIT	PAPER NUMBER
1637	

DATE MAILED: 04/15/2003

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/574,386	ALBERTSON ET AL.	
	Examiner	Art Unit	
	Alexander H. Spiegler	1637	

-- Th MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *11 December 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-25* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-25* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTQ-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

1. This action is in response to Paper No. 18, filed on December 11, 2002. Currently, claims 1-25 are pending. Applicants note in Paper No. 14 that claims 2 and 22 have been canceled, however, it does not appear that these claims were officially canceled. It is clear that claims 2 and 22 have been incorporated into amended claims 1 and 21, respectively. Thus, Applicants should cancel claims 2 and 22 in the next communication to the Office.

This action is made NON-FINAL. Any objections and rejections not reiterated below are hereby withdrawn. Specifically, the 112, 2nd paragraph rejections have been withdrawn in view of Applicants arguments.

Specification

2. Claims 2 and 22 are objected to under 37 CFR 1.75(c), for failing to further limit the subject matter of a previous claim. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form.

Claim Rejections - 35 USC § 112

3. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

4. Claims 19, 21-22 and 24 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 19, 21-22 and 24 are indefinite over "about 20%" because it is not clear as to

what the metes and bounds of this recitation are. The specification only refers to the specific concentration of 20% (see for example, pgs. 14 and 20) and does not set forth any definition or range of what is encompassed by "about 20%". Applicants can overcome this rejection by deleting "about".

Claim Rejections - 35 USC § 103

5. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

6. Claims 1-16, 20, 23 and 25 are rejected under 35 U.S.C. 103(a) as being unpatentable over Brown et al. (US 5,807,522, cited in the IDS), in view of Smith (PCR Methods and Applications (1992) 2: 21-27, cited in the IDS).

Brown teaches methods for fabricating microarrays of biological samples. Specifically, Brown teaches a method for forming a microarray comprising, dispensing a known volume of a reagent at a selected array position, by tapping a capillary dispenser onto a support under conditions effective to draw a defined volume of liquid onto the support (abstract). Therefore, Brown teaches a method form forming grid arrays (i.e., microarrays) comprising placing biological samples at discrete locations on said array (see cols. 3-5 and Figs 3-4 which teach the application of biological solutions to discrete locations on an array).

The reference teaches that the microarray can comprise immobilized polynucleotides (col. 11, 43-61 and col. 13 to col. 14, ln. 34). Brown teaches that these immobilized microarrays

can be used for "large scale hybridizations assays in numerous genetic applications, including genetic and physical mapping of genomes, monitoring of gene expression, DNA sequencing, genetic diagnosis, genotyping of organisms", etc. (col. 14, ln. 35 to col. 15, ln. 67). Brown also teaches that his method overcomes limitations of prior methods to array genomic fragments (col. 1, ln. 64 to col. 2, ln. 25). In one embodiment, Brown teaches the application of target solutions comprising amplified products to one or more substrates, wherein each target solution is applied to a distinct location on one substrate to produce an array of polynucleotides (col. 16, ln. 23-38 and col. 17, ln. 45-55).

Furthermore, Brown reference teaches that the volume of each target applied to the substrate is 0.01 to 100 nanoliters (col. 3, ln. 39-41), and the array can comprises at least 10^3 amplification products in a 1 cm^2 region of substrate (col. 4, ln. 16-19).

Accordingly, Brown teaches a method of preparing an array of polynucleotides, including preparing an array of amplified polynucleotide products.

Brown does not teach preparing an array of specific PCR products, such as those from a ligation-mediated PCR reaction.

However, Smith teaches the advantages of carrying out a ligation-mediated PCR reaction. Specifically, Smith teaches the advantages of performing ligation-mediated PCR is that "specific fragments can be isolated without any prior knowledge of the nucleotide sequence of the target" and furthermore, individual, unknown fragments can be amplified "from any DNA molecule ranging from about 50 to 250kb in size" (pg. 21).

Smith teaches ligation-mediated PCR of restriction fragments from large DNA molecules. Specifically, Smith teaches the method comprising,

a) providing a plurality of samples of double-stranded polynucleotide fragements, wherein each sample is derived from a first polynucleotide;

b) ligating adapters to each end of the polynucleotide fragments, wherein each adapter comprises a first strand and a second strand, the second strand having a region of substantial complementarity to a region of the first strand;

c) using sequences within the adapters to amplify the modified polynucleocids fragments to produce an amplification product for each sample of polynucleotide fragments, wherein each amplification product is representative of the first polynucleotide corresponding to each sample. (see abstract, pgs. 21-22, Table 1 and pg. 24)

Smith also teaches that the ligase-mediated PCR technique can be used in polynucleotides derived from large molecules, such as YAC (see abstract and pg. 25). With respect to claim 10, the reference teaches the use of a type IIS restriction endonucleases (abstract). With respect to claims 11-13, the reference teaches that the length of the double stranded sequence is 350 basepairs. Finally, Smith teaches that his PCR products can be used in arraying high-density grids (e.g., polynucleotide arrays) (pg. 26).

In view of the teachings of Smith, it would have been obvious to one of ordinary skill in the art at the time the invention was made to have modified the method of Brown so as to have included the steps of applying target solutions comprising amplification products from the ligation-mediated PCR reaction of Smith, in order to have achieved the benefits stated by Smith of providing an effective means of analyzing unknown DNA from large molecules, such as YACs.

Response to Applicants Arguments

The instant claims are drawn to a method of applying amplification products from a ligation-mediated amplification reaction onto a substrate at discrete locations. Applying amplification products to substrates (e.g., arrays) is well known in the art, as evidenced by the teachings of Brown (see above). Furthermore, ligation-mediated amplification reactions are also well known in the art; specifically ligation-mediated amplification reactions comprise amplifying double-stranded polynucleotide fragments using adaptors (as taught by Smith above). This is evidenced by Applicants admission that "The considerations for designing adapters suitable for use in the present invention do not differ from those in standard ligation-mediated amplification procedures. See...Smith" and that after ligation, the amplification can be carried out by the methods Smith (pgs. 12-13). Therefore, the method steps, e.g., steps a) to c), of the instant claims and those method steps recited by Smith are the same.

Applicants argue that Smith does not teach fragments that are representative of the starting polynucleotide, and only teach a fragment of a large DNA molecule, lambda DNA. However, Smith states,

> This ligase-mediated PCR technique was originally conceived as a way to generate representative sequencing template from large molecules, such as amplified YACS. Using the optimized protocols described here, it should indeed be possible to generate large numbers of unique fragments.

(pg. 25, col. 3).

Here, Smith states that the amplified products are representative of the starting polynucleotide, and that even if "unique amplified fragments" are generated, it does not take away from the fact that the fragments remain representative of the starting polynucleotide. Furthermore, the teaching of Smith outlines the exact steps of the claimed invention, and

therefore, the amplified products will have the same properties with respect to the starting polynucleotide of which they are derived from. It is also noted; Smith teaches his method can be carried out using large molecules, such as YACS (pg. 21 and 25).

As per Applicants second argument (motivation), the rejection has changed, and therefore, Applicants second argument is considered moot. As per Applicants third argument (reasonable expectation of success), a skilled artisan would have a reasonable expectation of success for applying the target solutions of Smith to the array of Brown. Brown specifically teaches applying PCR products to microarrays, and therefore, there is no reason to believe that the PCR products of Smith would not be able to be applied to a microarray.

7. Claim 17 is rejected under 35 U.S.C. 103(a) as being unpatentable over Brown et al. (US 5,807,522, cited in the IDS), in view of Smith (PCR Methods and Applications (1992) 2: 21-27, cited in the IDS), and in further view of Gordon et al. (US 5,601,980, previously cited).

The teachings of Brown and Smith are presented above. The references do not teach the spotting of the target solutions on the substrate.

Gordon et al. teaches a manufacturing method and apparatus for biological probe arrays using vision-assisted micropipetting. Specifically, Gordon teaches a robotically manipulated micropipette which is used for spotting biological samples onto an array (col. 3, ln. 59-60).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to have further modified the method of Brown and Smith so as to have robotically spotted target solutions onto the substrate (i.e. array) in order to have achieved the benefits stated by Gordon of providing an accurate and cost effective spotting of miniscule volumes of biological material onto a substrate.

8. Claim 18 is rejected under 35 U.S.C. 103(a) as being unpatentable over Brown et al. (US 5,807,522, cited in the IDS), in view of Smith (PCR Methods and Applications (1992) 2: 21-27, cited in the IDS), and further in view of Stimpson et al. (Proc. Natl. Acad. Sci. USA (1995) 92: 6379-6383, previously cited).

The teachings of Smith and Brown are presented above. The references do not teach the method wherein at least one of the adapters includes an amino group.

Stimpson teaches the method of real-time detection of DNA hybridization and melting on oligonucleotide arrays by using optical wave-guides. Specifically, Stimpson teaches DNA chips (i.e. array), which are constructed by using 3'-amino-labeled oligonucleotides (pg. 6380). Furthermore, Stimpson teaches that these amino-labeled oligonucleotides are immobilized onto the chip (pg. 6380).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to have further modified the method of Brown and Smith so as to have added an amino group to the adapter so as to have aided in the immobilization of the amplified polynucleotide onto the array.

9. Claims 19, 21-22 and 24 are rejected under 35 U.S.C. 103(a) as being unpatentable over Brown et al. (US 5,807,522, cited in the IDS), in view of Smith (PCR Methods and Applications (1992) 2: 21-27, cited in the IDS), and further in view of Cronin et al. (WO 97/43450, previously cited) or Pinkel et al. (USPN 5,837,196).

The teachings of Brown and Smith are presented above. The references do not teach resuspending the target solutions with dimethyl sulfoxide (DMSO) at a concentration of about 20% by volume.

However, Cronin and Pinkel teach that it is advantageous to resuspend a target solution in DMSO in a concentration of about 20% volume. Specifically, Cronin teaches that the addition of a denaturing agent, such as DSMO in a concentration of at about 20%, to hybridization and/or wash buffers "greatly improves signal resolution in hybridization assays performed on substrate-bound oligonucleotide arrays (pg. 2 and 5-6). Pinkel teaches that the addition of DSMO in a concentration of about 20% improves the attachment of nucleic acids to solid surfaces (col. 3, ln. 24-37 and cols. 11-12).

In view of the teachings of Cronin or Pinkel, it would have been obvious to one of ordinary skill in the art at the time the invention was made to have modified the methods of Brown and Smith so as to have included the steps of resuspending the target solution with DSMO in a concentration of at about 20%, in order to have achieved the benefits stated by Cronin of "greatly improv[ing] signal resolution in hybridization assays" or in order to have achieved the benefits stated by Pinkel of improving the ttachment of nucleic acids to sold supports.

Conclusion

10. No claims are allowable.

Correspondence

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Alexander H. Spiegler whose telephone number is (703) 305-0806. The examiner can normally be reached on Monday through Friday, 7:00 AM to 3:30 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's

supervisor, Gary Benzion can be reached on (703) 308-1119. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 308-4242 and (703) 305-3014. Applicant is also invited to contact the TC 1600 Customer Service Hotline at (703) 308-0198.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

Alexander H. Spiegler
April 10, 2003

KENNETH R. HORLICK, PH.D
PRIMARY EXAMINER
4/14/03